PI: Elias Sayour

Study Title: ACTION Trial: Adoptive Cellular Therapy following Dose-Intensified Temozolomide in Newly-diagnosed Pediatric High-grade Gliomas (Phase I)

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UF | Institutional Review Board
UNIVERSITY of FLORIDA

INFORMED CONSENT FORM
to Participate in Research, and

AUTHORIZATION
to Collect, Use, and Disclose Protected Health Information (PHI)

INTRODUCTION

If you are a parent or legally authorized representative for the subject, as you read the information in this Consent Form, you should put yourself in their place to decide whether or not to allow us to collect research information about them and to allow them to take part in this study. If the subject you are representing becomes able to understand the information in this Consent Form while they are still participating in the study, he/she must then decide on their own if he/she wants to continue to take part in this research study. As you read the rest of this form, the word "you" refers to the subject.

If you are an adult, child, or adolescent reading this form, the word 'you' refers to you.

Name of person seeking your consent:_____

Place of employment & position: _____

Please read this form which describes the study in some detail. A member of the research team will describe this study to you and answer all of your questions. Your participation is entirely voluntary. If you choose to participate you can change your mind at any time and withdraw from the study. You will not be penalized in any way or lose any benefits to which you would otherwise be entitled if you choose not to participate in this study or to withdraw. If you have questions about your rights as a research subject, please call the University of Florida Institutional Review Board (IRB) office at (352) 273-9600.

GENERAL INFORMATION ABOUT THIS STUDY

1. Name of Participant ("Study Subject")

_____

2. What is the Title of this research study? Adoptive Cellular Therapy following Dose-Intensified Temozolomide in Newly-diagnosed Pediatric High-grade Gliomas (Phase I)

3. Who do you call if you have questions about this research study?

Principal Investigator: Elias Sayour, MD, PhD at (352) 273-9000

Other research staff: Marcia Hodik at (352) 273-6971

For emergencies after hours or on weekends or holidays: Call (352) 273-9000 and ask to speak with the Neurosurgery Resident on call.

4. Who is paying for this research study?

The National Pediatric Cancer Foundation, the sponsor of this study, is paying for this study.

5. In general, what do you need to know about this Research Study?

Agreeing to become involved in any research is always voluntary. By signing this form, you are not waiving any of your legal rights. If you decide not to participate in this research, you will not be penalized in any way and you will not lose any benefits to which you are entitled. If you have questions about your rights as a research subject, please call the University of Florida Institutional Review Board (IRB) office at (352) 273-9600.

a) In general, what is the purpose of the research, how long will you be involved?

It is believed that the body's immune system protects the body by attacking and killing tumor cells. T-lymphocytes (T-cells) are part of the immune system and can attack when they recognize special proteins on the surface of tumors. But in most patients with advanced cancer, T-cells are not stimulated enough to kill the tumor. In this research study, we will use your tumor to make a vaccine which we hope will stimulate your T-cells to kill tumor cells and leave your normal cells alone.

High grade gliomas (HGGs) are very aggressive and difficult for the body's immune system to attack. Before T-cells can become active against tumor cells, they require strong stimulation by special "stimulator" cells in the body called Dendritic Cells (DCs) which are also part of the immune system. DCs can recognize the cancer cells and then activate the T lymphocytes, and create this strong stimulation.

The purpose of this research study is to learn whether anti-tumor T-cells and anti-tumor DC vaccines can be given safely. Most importantly, this study is also to determine whether the T-cells and DC vaccines can stimulate your immune system to fight off the tumor cells in your brain. When the vaccine for this study is made, dendritic cells will be loaded with genetic material called RNA (ribonucleic acid) from your tumor to stimulate the dendritic cells. The vaccine has two components given at different times after your initial radiation treatments with chemotherapy and then throughout your next 6 chemotherapy cycles. The first part, the DC vaccine, involves RNA loaded dendritic cells that are given under the skin at several time points in the study and the second part, xALT vaccine, is a single infusion of tumor-specific T cells delivered through one of two peripheral IV

catheters that are placed prior to xALT infusion. This vaccine is investigational which means that it is not approved by the US Food and Drug Administration (FDA) and is being tested in research studies.

It is hoped that by injecting the DC vaccine into your skin and infusing the xALT into your blood, your immune system will be activated against the tumor. Once it is activated against the tumor, your immune system may recognize and attack the tumor cells in your brain and not attack normal cells. Use of a vaccine that stimulates your immune system is called immunotherapy.

You are being asked to be in this study because you have a newly diagnosed, Grade III or IV High Grade Glioma (HGG). You are being offered participation in the study treatment arm of this study because you have been screened and deemed eligible by the study doctor. Some of these tests and procedures are part of your regular cancer care and may be done even if you don't join the study. Other tests will be done only because you are in this study. If you have had some of these tests or procedures done recently, they may not have to be repeated. This will be up to your study doctor.

We, the study doctors and researchers study diseases and other health problems people may have. Our goal is to try to find better ways to help treat these health problems. To do this, we sometimes ask people to take part in research studies.

If you have any questions about or do not understand something in this form, you should ask the study doctor or study staff. Discuss your participation with anyone you choose in order to better understand this study and your options. Do not sign this form unless the study doctor or study staff has answered your questions and you decide that you want to be part of this study.

Participating in a research study is not the same as getting regular medical care. The purpose of regular medical care is to improve your health. The purpose of a research study is to gather information. Being in this study does not replace your regular medical care.

It will be approximately 12 months from the time you agree to participate in this study until you complete vaccine therapy. After that, if your tumor has not progressed, you will be evaluated every other month for one year and then approximately every 6 months to check the status of your brain tumor. If your tumor progresses, we would like to collect information on how you are doing every 3 to 6 months for as long as you allow us to do so.

b) What is involved with your participation, and what are the procedures to be followed in the research?

Treatment on this study consists of three parts: 1) Surgery; 2) Radiation with chemotherapy added (chemoradiation); and 3) adjuvant Temozolomide (TMZ) chemotherapy with Immunotherapy. The immunotherapy with T-Cells and DCs (vaccine therapy) is the research portion of this study. During this study we will make, test and give the vaccine therapy. Before starting chemoradiation, you will undergo leukapheresis, a process similar to donating blood, to collect blood cells that are needed to make the vaccine. The procedure will take about 3-6 hours to

complete and will require you to have a central line (similar to infusion line) placed in a large vein in your neck. Placement of a central line may require a procedure (similar to an operation). The doctor performing the procedure may use special x-rays to assist with placement of the special IV. The central line will be removed after the cell collection is complete.

After chemoradiation, you will receive the first cycle of dose-intensified TMZ followed by three DC vaccines, each two weeks apart. You will also receive at tetanus vaccine (Td) with vaccine #1 and a smaller dose of Td at the vaccine site prior to DC vaccines #3, #6, and #8. Two weeks after the third DC vaccine, you will undergo a second leukapheresis to collect additional blood cells to make more DCs and xALT. You will then receive an additional five cycles of TMZ with monthly DC vaccinations. After completing your sixth TMZ cycle, you will receive three more DC vaccines, each two weeks apart, and a single infusion of x ALT.

As part of this study, we will collect blood samples for research at different timepoints before, during and after vaccine therapy. We will use these samples to see how the immune system is recovering after transplant and to learn more about the way the immune system's T-cells are working in your body and the effects of treatment.

c) What are the likely risks or discomforts to you?

While in this study, you are at risk for possible side effects from the study vaccine and the study procedures. You should discuss these with the study doctor. Side effects will vary from person to person and there may also be other side effects that you experience that were not predicted.

Side effects may be associated with chemoradiation, adjuvant TMZ chemotherapy and/or vaccine therapy. Possible side effects from vaccine therapy are rare and may include allergic reaction, swelling of the brain, low-blood pressure, difficulty breathing or in very rare occasions, death.

Risks of leukapheresis include light-headedness, fainting, vomiting, rapid breathing, chills, tingling, and nausea, blood clots. Placement of the large IV in the central vein in your neck can cause discomfort/pain, bruising, bleeding, and very rarely, injury to adjacent organs. The doctor placing the special IV will discuss these risks with you and you will sign a separate procedural informed consent form.

d) What are the likely benefits to you or to others from the research?

The study vaccine may allow your immune system to better fight your tumor, although it is possible that you will not benefit directly from this study. Information gained from this study may help doctors advance the medical treatment for brain tumors.

e) What are the appropriate alternative procedures or courses of treatment, if any, that might be helpful to you?

If you do not participate in this research study, you normal clinical care may include surgery, chemotherapy, and radiation. You may also choose to participate in another research study, if one is available and you qualify. You can also elect to have treatment of your symptoms only through supportive care.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Additional and more detailed information is provided within the remainder of this Informed Consent form, please read before deciding if you wish to participate in this study.

WHAT CAN YOU EXPECT IF YOU PARTICIPATE IN THIS STUDY?

6. What will be done as part of your normal clinical care (even if you did not participate in this research study)?

If you choose not to participate in this research study, your normal clinical care would include radiation with or without chemotherapy during and after radiation therapy. Your treating radiation oncologist and/or neuro-oncologist will determine this therapy plan.

7. What will be done only because you are in this research study?

Making the Vaccine

Before starting radiation with chemotherapy added (chemoradiation) and two weeks after Cycle 1 (described below), you will undergo leukapheresis, a process similar to donating blood, to collect blood cells that are needed to make the vaccine. The leukapheresis procedure will be performed and will take from 3 to 6 hours and may take up to three collection days to accomplish to get enough cells to make the DC and xALT products. The collected cells will be delivered to a laboratory and used to make the DC vaccine and xALT infusion. Once made, both are frozen for later use. If we are unable to make the full amount of xALT and/or DCs, you will still receive what we were able to make, which could be a smaller dose or no dose at all of one of the vaccines.

Testing the Vaccine

Before the study vaccine can be given to you, a small sample of the xALT and DCs will be tested in the lab to make sure they can be given safely. If one or both of them do not meet all requirements for administration, which is unlikely, you would only receive the part of the vaccine that passed testing.

Giving the Vaccine

After chemoradiation, you will receive the first cycle of dose-intensified Temozolomide (TMZ) followed by three DC vaccines, each two weeks apart. DC vaccine will be given as an injection at day 22-24 after the first TMZ cycle. An equal amount of vaccine will be given in each groin area. Each injection will only take a few minutes and, if you are an outpatient, you will be monitored for 30 minutes after each injection to be certain you are not having any reactions. You will receive tetanus vaccine (Td) booster (5 Lf) with immunotherapy vaccine #1 even if you have had a tetanus vaccine in the past. Additionally, you will receive a smaller dose of Td at the vaccine site prior to immunotherapy vaccine doses #3, #6, and #8. Two weeks after the third DC vaccine, you will undergo a second leukapheresis to collect additional blood cells to make more DCs and xALT. You will then receive an additional five cycles of TMZ with monthly DC vaccinations. Each monthly DC vaccine will be administered 24-72 hours after completing each 21-day course of dose-intensified TMZ. After completing your sixth TMZ cycle, you will receive three more DC vaccines, each two weeks apart, and a single infusion of x ALT. You will be monitored for 1 hour after the xALT infusion to be certain you are not having any reactions.

WHAT HAPPENS WHEN I COME FOR STUDY VISITS?

After you sign this form, the study doctor or study staff will do the things listed below when you come in for study visits. If you would like more information about which tests and procedures will be done at each study visit, ask the study doctor or study staff. During vaccine therapy, you will be evaluated approximately every month. After vaccine therapy is complete, you will be evaluated every other month for one year, then every 3 to 6 months thereafter. During these visits, you will receive a number of routine tests to watch for side effects and check the status of your brain tumor.

- **Demographic Questions:** Ask you to give personal information, such as your name, date of birth, race, etc.
- **Health and Medication Questions:** Ask you to answer questions about your health, your medical history, and the medications you take
- **Physical Exam:** You should ask the study doctor about what will happen during this exam.
- **Performance Status (Lansky or Karnofsky):** You will be asked some questions to determine how your disease is progressing and how the disease affects the quality of your life
- **Height, Weight:** See how tall you are, and see how much you weigh
- **Blood Testing:** Take some blood to do laboratory tests to check on your health
- **Research Samples:** The study team will collect blood samples for research. We will use these samples to see how the immune system is recovering and to learn more about the way the immune system's T-cells are working in your

body and the effects of study treatment. We will collect 10-15cc (no more than 1 tablespoon) of blood. This peripheral blood will be drawn prior to each leukapheresis, TMZ cycles, and vaccinations, post xALT infusion on days 1 and 4, and during follow up visits if feasible. If possible, this blood will be collected at the same time blood is collected for routine testing.

- **Blood Tests including HIV and Hepatitis Testing**
  Before and after leukapheresis, blood will be collected for routine laboratory tests. These tests will check your blood counts, kidney and liver function, salts in the blood, and your blood's ability to form clots. Blood tests to check to see if you have ever been infected with any viruses that can be transmitted through the blood will also be checked. These tests include but not limited to: Human immunodeficiency virus (HIV), syphilis, hepatitis B or C, and Cytomegalovirus (CMV). The results of these tests will be shared with you and you will be counseled as to the meaning of the results, whether they are positive or negative. If you do not want to be tested for HIV or Hepatitis, then you should not participate in this study. In this study, HIV and Hepatitis testing is to make sure you do not have any infections in the blood that may alter your response to the study vaccine.

- **Leukapheresis:** Some blood will be removed from your veins and processed by a machine to remove a small portion of the white cells. The volume of blood that you actually will lose is about 6 tablespoons. This procedure is called "apheresis."

  The apheresis procedure requires inserting an intravenous needle into your arm or placing a special IV called a central venous catheter in your neck for the collection of these white blood cells. Placement of a central line may require a procedure (similar to an operation) and may be done with anesthesia or conscious sedation. Conscious sedation lets you recover quickly and return to your everyday activities soon after your procedure. Anesthesia is a drug or agent used to decrease the feeling of pain, or eliminate the feeling of pain by putting you to sleep. You will receive these medicines through an intravenous line (IV, in a vein most likely in your arm). The doctor may use special x-rays (called fluoroscopy) to assist with IV placement of the central line. This involves quick, low amounts of radiation. The catheter will be held in place by stitches in the skin. The apheresis procedure will last approximately three to six hours. The apheresis machine divides whole blood into white cells (which fight infection), plasma (the liquid part of the blood) and red cells (which carry oxygen). The lymphocytes are a part of the white cells, and a small portion of your lymphocytes will be permanently removed by the machine. The red cells, plasma and remaining white cells will be returned to you. During the procedure, you will be asked to remain as still as possible. The central line will be removed after the cell collection is complete. Pressure will be applied at the catheter insertion location for 5-10 minutes (maybe longer) and an occlusive bandage will be applied. These cells will be used for PBSC infusion and to make the investigational vaccine for this study. You will undergo a second

leukapheresis after Vaccine #3 to collect additional cells to make more investigational vaccine.

- **Filgrastim (G-CSF) Injections**

  In order to increase the number of peripheral stem cells (PBSC's) collected, you will be given a medication called Filgrastim (G-CSF). G-CSF is given as a subcutaneous (under the skin) injection for approximately 4-14 days before the mobilized collection (first leukapheresis procedure). G-CSF stimulates the growth of white blood cells in the bone marrow and draws white blood cells, including PBSCs, from the bone marrow into the blood.

- **MRI Scan:** Magnetic resonance imaging (MRI) is a procedure that allows doctors to look inside the body by using a scanner that sends out a strong magnetic field and radio waves. This procedure is used routinely for medical care and is very safe for most people, but you will be monitored during the entire MRI scan in case any problems occur. You may have to read and sign a separate consent form before you can have an MRI.

- **Tetanus Toxoid Booster**: Before your first dose of immunotherapy, you will be given a standard tetanus shot into a muscle of the upper arm. After that a smaller dose of tetanus will be given at the vaccine site prior to Vaccine #3, #6, and #8.

STUDY TREATMENT

Treatment on this study consists of three parts: 1) Surgery 2) Chemoradiation 3) Adjuvant TMZ chemotherapy with Immunotherapy.

Chemoradiation

TMZ should be administered continuously from day 1 of radiotherapy to the last day of radiation at a daily oral dose of 90 mg/m2 radiation for a maximum of 49 days. This medication is taken 1 hour prior to radiation and in the morning on non-radiation days.

Study Drug Name	Route	Dose	Schedule
Temozolomide	PO	50mg/m^2/day-100mg/m^2/day based on tolerance	Days 1-21, 6 cycles
Adoptive Tumor-specific T cells (xALT)	IV	Target dose of 3x10^{8}cells/kg or all available cells	Day 23-25 **Cycle 6 only**
TTRNA-loaded DCs (10 vaccines-V1-10)	Intra-dermal ID	1x10^7 cells/kg	V1: Cycle 1 Day 22-24 V2: Cycle 1 Day 36-38 V3: Cycle 1 Day 50-52 V4: Cycle 2 Day 22-24 V5: Cycle 3 Day 22-24

			V6: Cycle 4 Day 22-24 V7: Cycle 5 Day 22-24 V8: Cycle 6 Day 23-25 V9: Cycle 6 Day 37-39 V10: Cycle 6 Day 51-53
Sargramostim (GM-CSF)	ID	150ug Embedded within each vaccination of TTRNA-loaded DCs	Concurrent with each DC vaccine (V1-V10) as above
Tetanus/diphtheria vaccination	IM/ID	V1: 0.5 ml V3, V6, & V8 0.1 ml	V1: 0.5 ml V3, V6, & V8 0.1 ml
Filgrastim(G-CSF)	IV/SQ	10 micrograms/kg/day (max dose of 480 mcg/day)	Prior to leukapheresis #1

Adjuvant Therapy

WHILE YOU ARE IN THE STUDY (including follow up period), YOU MUST:

- Follow the instructions you are given.
- Come to the study center for all visits with the study doctor.
- Give correct and accurate information about your medical history and current medical condition.
- Tell the study doctor about any health problems you have during the study.
- Tell the study doctor about any new medicine or drug you take during the study.
- Not take any other drugs or remedies unless the study doctor has approved them beforehand. This includes investigational drugs, prescription drugs and over the counter medicine (including vitamins and herbal remedies) that you buy without a prescription.
- Not participate in other medical research studies.
- Not get pregnant or cause your partner to become pregnant
- Tell the study doctor or study staff if you want to stop being in the study at any time.

Information about you (demographics), your medical history, the progress of your treatment at UFHealth on this study, side effects you may have, your responses to treatment, and laboratory information about your DC vaccine and vaccinations will be collected and sent to the Moffitt Cancer in Tampa, FL. The Moffitt Center is the Central Coordinating Center that collects all information about people treated on this study, whether they are at UFHealth in Gainesville or elsewhere. The information sent to the Moffitt Coordinating Center is handled with strict information security safeguards and is maintained in secure computer systems.

Once this research study is completed, any information that could identify you **might** be removed from any identifiable private information or identifiable biospecimens collected and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you or your legally authorized representative.

If you have any questions now or at any time during the study, please contact one of the research team members listed in question 3 of this form.

8. How long will you be in this research study?

It will be approximately 12 months from the time you agree to participate in this study until you complete vaccine therapy. After that, if your tumor has not progressed, you will be evaluated every other month for one year and then approximately every 6 months to check the status of your brain tumor. If your tumor progresses, we would like to collect information on how you are doing every 3 to 6 months for as long as you allow us to do so.

If your tumor comes back, you may have a biopsy of the tumor as part of your routine clinical care. If you have a biopsy and extra tissue is available, we will use some of the tissue that is removed to see how well the vaccine worked in that tissue as a part of this research study.

9. How many people are expected to take part in this research study?

Approximately 12-18 participants from 3 medical centers in the United States will take part in this study. Up to 10 participants may take part in this portion of the study at the University of Florida.

WHAT ARE THE RISKS AND BENEFITS OF THIS STUDY AND WHAT ARE YOUR OPTIONS?

10. What are the possible discomforts and risks from taking part in this research study?

While in this study, you are at risk for possible side effects from the study vaccine and the study procedures. You should discuss these with the study doctor. Side effects will vary from person to person and there may also be other side effects that you experience that were not predicted. Many side effects go away shortly after the drug is stopped, but in some cases, side effects may be serious, long lasting, and/or permanent and may even cause death.

Leukapheresis

Some side effects associated with the leukapheresis procedure may be similar to those experienced during blood donation and include light-headedness, fainting,

vomiting, and rapid breathing. Other side effects which may occur that are unique to the leukapheresis procedure include chills caused by cooling of the blood when it is contained in the special machine, and tingling and nausea caused by low blood calcium levels due to the blood thinner (called citrate) used to maintain free flow of the blood through the machine. These side effects can be controlled by altering the rate at which blood is withdrawn, by warm blankets, by altering the amount of blood thinner, by administration of calcium during the procedure, and by stopping the procedure. Rarely, the leukapheresis procedure may be associated with loss of blood, breakdown of the blood, clotting of the blood, allergic reactions, inadvertent infusion of air, and fluid overload or depletion. These side effects can usually be controlled by stopping the procedure and providing appropriate medical care. In addition, there is always the risk that very uncommon or previously unknown side effects may occur or that life-threatening side effects may occur and death may result.

Central Venous Catheter Insertion for leukapheresis

The doctor placing the catheter will describe the procedure and risks of the procedure and ask you to sign a separate consent form before the catheter placement.

The risks of central catheter placement associated with this deeper venous catheter include:

- bruising around the catheter,
- injury to the vein or other blood vessels, nerves and/or organs close to the area of catheter placement,
- collapse of the lung, bleeding or fluid in the chest that could require chest tube placement,
- bleeding under the skin,
- infection,
- allergic reaction to local numbing medication,
- irregular heartbeat,
- clotting of the catheter or the blood vessel or irritation/redness of the vein.
- narrowing of the vein which may prevent future use of the vessel
- removal of the central venous catheter may cause discomfort, small amount of bleeding and pressure will need to be held in the area for 5-10 minutes (maybe longer).

There is also a very rare possibility that you may have symptoms ranging from dizziness and fainting to allergic reactions such as anaphylaxis.

The radiation you will receive from the placement of the central line exposes a part of your body to a higher level of radiation than the rest of your body. The typical radiation exposure from this procedure is about 200 μSv (20 millirem) which is equal to about 26 days of natural background radiation exposure.

Conscious sedation/anesthesia risks:

There are risks to receiving conscious sedation or anesthesia. If sedation medication is given to helps reduce anxiety, discomfort, and pain during certain procedures, it will be given through an IV or by mouth. You may feel pain from the initial needle stick

when placing the IV. Possible bruising from where the needle went into the skin may occur, as well as rarely, an allergic reaction to the medication. Vomiting or inhaling food contents from the stomach are also risks of sedation. These risks are reduced if you do not eat for a minimum of 6-8 hours prior to any procedure. Sedation medications can also make you feel drowsy (sleepy), cause you not to remember the procedure, lower your blood pressure, slow or effect your breathing (respiratory depression) or rarely, lead to death. Risks of anesthesia may include complications such as breathing difficulties, low blood pressure, or an irregular heartbeat, which can rarely lead to death. The doctor performing this procedure will explain the risks and you will be asked to sign a separate consent.

Immunotherapy with T-cells and DCs (vaccine therapy)

The vaccine may cause an allergic reaction that can include redness or swelling at the injection site, itching, hives, low-blood pressure, difficulty breathing, or in rare occasions, death. The vaccine may cause a dramatic increase in the number of immune cells in the brain. This may cause swelling (edema) of the brain. Symptoms of swelling of the brain include severe headaches, confusion, lack of energy, unconsciousness, coma, and/or losses of movement, sensation, and/or function in certain areas of the body. Brain swelling may require treatment with medications and/or surgery.

The vaccination may activate the immune system to such a high degree that the immune system may start to attack normal brain tissue or other tissues in the body, although this is very unlikely.

There may be a small risk of infection due to potential contamination of the vaccination during the manufacturing or mixing process. This may result in redness, swelling, and/or irritation at the injection site. There may also be risks with the use of this vaccine that are not yet known.

The risks associated with the injection of autologous lymphocytes for immunotherapy in humans are currently unknown.

Temozolomide (TMZ)

Risks and side effects related to Temozolomide include those which are:

Likely:	**Less Likely:**	**Rare, but Serious:**
• Fewer red and white blood cells and platelets in the blood. A low number of red blood cells can make you feel tired and weak. A low number of white blood cells can make it easier to get	• Temporary tiredness • Nausea • Vomiting • Loss of appetite • Sores in mouth or on lips • Diarrhea • Fluid buildup in legs and arms	• Seizures • Dizziness • Memory-loss • Trouble falling asleep • Depression • Muscle aches • Blurred or double vision • Difficulty walking

infections. A low number of platelets cause you to bruise and bleed more easily.	• increased need to urinate • Hair loss • Liver damage	• Confusion • Difficulty swallowing • Partial paralysis or weakness of one side of the body • Blood clots which may be life-threatening • Allergic reaction/rash

Sargramostim (GM-CSF)

Risks and side effects related to the Sargramostim (GM-CSF) include those which are:

Likely:	Less Likely:	Rare, but Serious:
• Headache • Bone pain • Muscle and joint pains • Fever and Chills • Rash and itchiness • A feeling of discomfort or not feeling well and/or tiredness	• Stomach or abdominal pain or cramps • Weakness • Loss of appetite • Nausea and/or vomiting • Diarrhea • Excessive sweating • Inflammation of a vein through which the drug was given • Redness and pain at the injection site • Weight gain • Fewer platelets in the blood. A low number of 24 causes you to bruise and bleed more easily • Increase in the blood of certain enzymes or bilirubin (a substance that comes from the liver breaking down waste products) which could indicate liver irritation or damage • Elevation in the blood of creatinine which normally is removed from the blood by the kidney and could indicate kidney damage • Fluid build-up in the tissues usually of the lower legs	• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, and a rapid heart beat • A severe reaction which can cause shortness of breath, a low blood pressure, a rapid heart rate, fever, a feeling of warmth and back pain which may occur only with the first dose and not with further doses • An abnormally rapid heat beat • Leakage of fluid into the lungs which may result in shortness of breath and difficulty breathing and/or leakage of fluid into body tissues with puffiness of legs, arms or abdomen, weight gain and a drop in blood pressure • Inflammation of the lungs which may lead to pain and shortness of breath

		• A build-up of fluid around the heart which may be painful

Tetanus Toxoid Booster

The most common symptom is mild pain and tenderness at the site of injection. The most frequently reported general adverse reactions are irritability, fever, diarrhea, fatigue, diminished appetite, and rhinitis (stuffy or runny nose). Itching, hives, low-blood pressure, difficulty breathing, or in rare occasions death are all symptoms of anaphylaxis, which occurs within the first few hours after vaccination, is rare, and medication will be available to counteract these effects.

Filgrastim (G-CSF)

The most common but unlikely symptoms are local irritation (skin) at the injection site, ache or pain inside the bones, increased liver enzymes, uric acid levels in the blood and decreased number of platelets in the blood. Rare, but serious symptoms are allergic reaction, fever, enlargement of spleen, worsening of pre-existing skin rashes, temporary hair loss and inflammation of the blood vessels in the skin.

RISKS ASSOCIATED WITH STANDARD OF CARE OR ALTERNATIVE TREATMENT:

As with any medication or chemotherapy treatment, there may be risks, known and unknown.

The most common temporary side effects for **some** chemotherapy drugs may include nausea and vomiting, loss of appetite, hair loss, mouth sores, higher risk of infection (due to decreased white blood cells), bruising or bleeding, fatigue (feeling tired), and changes in your menstrual cycle if you are a woman, (such as, irregular periods to symptoms of menopause [end of menstruation]).

A more complete listing of side effects for other therapies may be available for you to review if you wish. Please talk with your study doctor about the risks of both this investigational drug and any alternative methods of treatment that are available.

WHAT CAN HAPPEN IF I GET INFUSIONS

You will receive study drug intravenously, which means you will receive it directly into your vein. This may cause the following problems:

- Irritation of the vein, your skin near the vein could become warm, swell, hurt, or get red
- Damage your vein
- Damage to the skin or tissue around the injection site
- Too much of the study drug may be given to you
- Increase or decrease in electrolyte levels (the amount of certain salts and other chemicals in your blood), causing health problems

- A blood clot or an air bubble could form, which could block a blood vessel in another part of your body

Some of these problems could be very serious.

Overtime, getting a lot of injections can cause a vein to become hard or scar, which can make it difficult to put a needle into the vein to give you a shot or take blood.

COULD I HAVE AN ALLERGIC REACTION

Injection of may result in an allergic reaction. If you have a very bad allergic reaction, you could die.

Some things that happen during an allergic reaction are:

- Redness and swelling at the injection site
- Itching
- Hives
- Low blood pressure
- Difficulty breathing

In addition, if the immune system becomes overly activated, potential discomforts may include pain, redness and swelling at the injection site.

You may experience an allergic reaction to preserved cells or other transfusion associated side effects such as

- Pain at the injection site
- Mild swelling or edema
- Hypotension (low blood pressure)
- Shortness of breath.

You should get medical help and contact the study doctor or staff if you have any of these or other side effects during the study.

IS THERE ANY RISK TO YOUR UNBORN CHILDREN IF YOU TAKE PART IN THIS STUDY?

For Women

If you are pregnant, you cannot participate in this study because there may be risks to you and your unborn baby. Breastfeeding (nursing) mothers will not be included in this study, since it is not known whether the drugs in this study will be passed on to the baby in mother's milk. If you are currently breastfeeding and wish to continue breastfeeding, your study doctor may recommend another treatment.

If you are female of child bearing potential (able to become pregnant), then you will be given a pregnancy test before beginning any study drug.

Tell the study doctor right away if:

- You are pregnant
- You become pregnant

- You are planning to become pregnant
- You are breastfeeding

For Men

We do not know what the study drug could do to your sperm. Should you get a woman pregnant, there could be harm to the unborn baby. You and your partner should use an effective form of birth control if your partner is a woman of childbearing potential.

For Men and Women

Whether you are a man or a woman, there may be risks to your unborn children that we don't know about ahead of time; they are unforeseeable.

If you take part in this study, you must use an effective birth control method as discussed with your study doctor during study treatment and continue to use it until at least 180 days after your last dose of study drug.

Examples of birth control methods include:

- Oral birth control pills
- Birth control patch
- Implanted (injectable contraceptive hormones or mechanical products such as intrauterine device
- Barrier methods (such as: diaphragm, condoms, or spermicides)
- Tubal ligation or vasectomy
- Abstinence (no sexual intercourse)

You should discuss the method of birth control which is best for you to use both during study treatment and for a minimum of 6 months after study treatment.

Whether you are a woman or a man, you should tell your study doctor immediately if you become pregnant or if your partner becomes pregnant. Women who become pregnant during the study will have to leave the study. The study doctor or study staff may ask for information about the pregnancy and the birth of the baby. The study doctor or study staff may share this information with the sponsor and Chesapeake IRB (a group of people who review research studies to protect the rights and welfare of research participants).

The long-term effects of the study drug on fertility are unknown. This means that it is unknown if the study drug will affect your ability to have children in the future. If we find out that the study drug might harm your fertility, we will explain what tests or procedures to follow for stopping the study drugs.

Cancer treatment can affect fertility in both men and women, and it is important to understand the risks before starting therapy. Ask your staff about fertility preservation before you begin study treatment. However, once you have started study treatment you should not donate or sell your eggs or sperm.

COULD I HAVE ANY OTHER PROBLEMS WITH MY HEALTH IF I DO THIS RESEARCH STUDY?

It is possible that you could have problems and side effects of immunotherapy that nobody knows about yet, which include your cancer getting worse or even death. If the study doctor learns any new information about the study drugs that might change your mind about continuing in the study, the study doctor or study staff will tell you about it. The study doctor will also tell you if new treatments become available for your cancer.

What are the risks of giving blood for this study?

The study doctor or study staff will take your blood by sticking a needle in your arm.

Some problems you might have from this are:

- Pain or discomfort at the site of puncture
- Bruising or swelling around the puncture site
- Dizziness or faintness from the procedure
- Infection

Ask the study doctor or study staff how much blood you will give during this study.

What are the risks of other study procedures?

- **MRI:** For most people, there is no danger associated with having an MRI scan.

  The MRI scanner contains a very strong magnet. Therefore, you may not be able to have the MRI if you have any type of metal implanted in your body, for example, any pacing device (such as a heart pacer), any metal in your eyes, or certain types of heart valves or brain aneurysm clips. Someone will ask you questions about this before you have the MRI. You must tell the study doctor about any objects that you know are implanted or imbedded in your body.

  There is not much room inside the MRI scanner. You may be uncomfortable if you do not like to be in close spaces ("claustrophobia"). During the procedure, you will be able to talk with the MRI staff through a speaker system, and, in the event of an emergency, you can tell them to stop the scan.

  The MRI scanner produces a loud hammering noise, which has produced hearing loss in a very small number of patients. You will be given earplugs to reduce this risk.

  If you are a woman of childbearing potential, there may be unknown risks to the fetus. Therefore, before you can have the MRI, you must have a pregnancy test.

  During each MRI, contrast will be given to help better see whether any tumor is present. Contrast is given routinely to obtain better MRI scans of the brain. It is administered through the vein and requires the placement of a catheter in your vein. The catheter placement is similar to drawing blood except that the catheter remains in the vein during the time the contrast agent is delivered. The risks of a blood draw and insertion of a catheter are similar. There have been a few, rare cases of allergies to the agent used in MRI contrast. Participants with allergies

(such as rash) may be given Tylenol and Benadryl prior to injection of the contrast.

A rare but serious adverse reaction has been observed in patients that received a gadolinium-based contrast material during MRI examinations, a reaction called nephrogenic systemic fibrosis (NSF). Patients with kidney disease are at increased risk of developing NSF. NSF may cause skin thickening, joint pain and/or swelling. In rare cases NSF can lead to lung and heart problems and cause death. To minimize the likelihood that you will be affected, you will have a blood test to measure your kidney function. If your blood test is abnormal, you will not be permitted to receive gadolinium.

WHAT IF I GET HURT OR SICK WHILE I AM IN THIS STUDY?

If you need emergency care:

- Call 911 or go to your nearest emergency room right away.

If you do NOT need emergency care:

- Call or go to your regular doctor. It is important that you tell your regular doctor that you are participating in a research study. If possible, take a copy of this consent form with you when you go.

If you experience a side effect or a change in the way that you feel, call the study doctor at the telephone number listed on the first page of this form.

By signing this informed consent and research authorization form, you have not given up any legal rights to seek compensation for injuries from the sponsor**.**

Researchers will take appropriate steps to protect any information they collect about you. However, there is a slight risk that information about you could be revealed inappropriately or accidentally. Depending on the nature of the information, such a release could upset or embarrass you, or possibly affect your insurability or employability. Questions 17-21 in this form discuss what information about you will be collected, used, protected, and shared.

This study may include risks that are unknown at this time.

Participation in more than one research study or project may further increase the risks to you. If you are already enrolled in another research study, please inform one of the research team members listed in question 3 of this form or the person reviewing this consent with you before enrolling in this or any other research study or project.

Throughout the study, the researchers will notify you of new information that may become available and might affect your decision to remain in the study.

If you wish to discuss the information above or any discomforts you may experience, please ask questions now or call one of the research team members listed in question 3 in this form.

11a. What are the potential benefits to you for taking part in this research study?

This study is not designed to benefit you directly. The reason for doing this study is to test the safety of DC vaccines and xALT given to people with high grade gliomas. Direct benefit to you is possible. The study vaccine may allow your immune system to better fight your tumor. If your immune system can better fight your tumor, your tumor may improve and you may feel better and/or live longer; however, your cancer might not get better or may even get worse while you are in this study.

11b. How could others possibly benefit from this study?

Information from this study might help researchers to come up with new tests or medications to help others in the future.

11c. How could the researchers benefit from this study?

In general, presenting research results helps the career of a scientist. Therefore, the Principal Investigator listed in question 3 of this form may benefit if the results of this study are presented at scientific meetings or in scientific journals.

12. What other choices do you have if you do not want to be in this study?

You do not have to be in this study to get help for your cancer. Alternative treatments for your cancer could include further surgery, chemotherapy, and radiation. You may also choose to participate in another research study, if one is available and you qualify. You can also elect to have treatment of your symptoms only through supportive care. The study doctor will talk to you about other things you can do for your cancer, including the important risks and benefits.

Your participation in this study is voluntary. You can decide not to be in the study and you can change your mind about being in the study at any time. There will be no penalty to you, and you won't lose any benefits. Your regular medical care at this study center will not change if you decide not to be in the study.

13a. Can you withdraw from this study?

You are free to withdraw your consent and to stop participating in this study at any time. If you do withdraw your consent, you will not be penalized in any way and you will not lose any benefits to which you are entitled.

If you decide to withdraw your consent to participate in this study for any reason, please contact one of the research team members listed in question 3 of this form. They will tell you how to stop your participation safely.

If you have any questions regarding your rights as a research subject, please call the Institutional Review Board (IRB) office at (352) 273-9600.

13b. If you withdraw, can information about you still be used and/or collected?

If you do withdraw your consent, information collected up until the time of your withdrawal will be used; however, no additional information will be collected. If you or the study doctor decides to stop your treatment early, we will continue to follow you to monitor your tumor and any adverse events (a bad effect) related to the study; however, if you decide that you do not want to be followed, we will not collect any additional information. If your tumor progresses or an adverse event occurs, we may need to review your entire medical record.

13c. Can the Principal Investigator withdraw you from this study?

You may be withdrawn from the study without your consent for the following reasons:

- We are unable to make or give the vaccine
- You do not follow the instructions given to you by the research staff
- You experience a side effect and your physician feels it would be in your best interest to stop study treatment
- You have a positive pregnancy test
- The study is stopped

WHAT ARE THE FINANCIAL ISSUES IF YOU PARTICIPATE?

14. If you choose to take part in this research study, will it cost you anything?

Study Drugs

TTRNA-DC with GM-CSF and it's administration will be provided at no cost to you while you are participating in this study.

TTRNA-xALT, Hematopoietic Stem Cells (if given), Tetanus/diphtheria (Td), and Filgrastim (G-CSF) will be provided at no cost to you while you are participating in this study. However, the cost of administering the TTRNA-xALT, Hematopoietic Stem Cells, Tetanus/diphtheria (Td), and Filgrastim (G-CSF) will be billed to you or your insurance company. You will be responsible for paying any deductible, co-insurance, or co-payments for these services, and for any non-covered or out-of-network services.

The cost of Temozolomide (TMZ), radiotherapy, and all other treatments will be billed to you or your insurance company. You will be responsible for paying any deductible, co-insurance, or co-payments for these services, and for any non-covered or out-of-network services.

Study Services

The Sponsor will pay for or provide the following study-required services/activities at no cost to you:

1. Performance status
2. Tumor tissue for TTRNA extraction
3. Leukapheresis to (Harvest autologous stem cells)
4. Extra office visits only for TTRNA-DC injection by study coordinator
5. Immune monitoring studies

If you receive a bill for these services, please contact Dr. Sayour at 352-273-9000.

Items/Services Not Paid for by the Sponsor

All other medical services you receive would have been provided to you even if you were not in this study. These services will be billed to you or your insurance company in the usual manner. You will be responsible for paying any deductible, co-insurance, co-payments, for those services, and for any non-covered or out-of-network services.

Some insurance companies may not cover costs associated with studies. Please contact your insurance company for additional information.

15. Will you be paid for taking part in this study?

You will not be paid for your participation in this study.

16. What if you are injured because of the study?

If you are injured as a direct result of your participation in this study, only the professional services that you receive from any University of Florida Health Science Center healthcare provider will be provided without charge. These healthcare providers include physicians, physician assistants, nurse practitioners, dentists or psychologists. Any other expenses, including Shands hospital expenses, will be billed to you or your insurance provider.

You will be responsible for any deductible, co-insurance, or co-payments. Some insurance companies may not cover costs associated with research studies or research-related injuries. Please contact your insurance company for additional information.

The Principal Investigator will determine whether your injury is related to your participation in this study.

No additional compensation is routinely offered. The Principal Investigator and others involved in this study may be University of Florida employees. As employees of the University, they are protected under state law, which limits financial recovery for negligence.

Please contact Dr. Sayour or the study coordinator at 352-273-9000 if you experience an injury or have questions about any discomforts that you experience while participating in this study.

17. How will your health information be collected, used and shared?

We understand that information about you and your health is personal, and we are committed to protecting the privacy of that information. Because of this commitment and because of federal law, we must obtain your written authorization before we use or disclose your information for this study.

If you agree to participate in this study, the Principal Investigator will create, collect, and use private information about you and your health. This information is called protected health information or PHI. In order to do this, the Principal Investigator needs your authorization The following section describes what PHI will be collected, used and shared, how it will be collected, used, and shared, who will collect, use or share it, who will have access to it, how it will be secured, and what your rights are to revoke this authorization.

Your protected health information may be collected, used, and shared with others to determine if you can participate in the study, and then as part of your participation in the study. This information can be gathered from you or your past, current or future health records, from procedures such as physical examinations, x-rays, blood or urine tests or from other procedures or tests. This information will be created by receiving study treatments or participating in study procedures, or from your study visits and telephone calls. More specifically, the following information may be collected, used, and shared with others:

- Information that identifies or could be used to identify you such as name, date of birth, address, telephone numbers, medical record number and exact dates collected from your past, current or future health records
- Complete past medical history
- Records of physical and neurological exams, performance status, height, weight and other procedures you have during the research
- Laboratory, pathology, radiology, MRI and other test results
- HIV and other infectious disease test results
- Records about medications and radiation therapy for your tumor and/or other conditions
- Ability or potential ability to conceive a child
- Records about side effects or adverse experiences you may experience

This information will be stored in locked filing cabinets or on computer servers with secure passwords, or encrypted electronic storage devices.

Some of the information collected could be included in a "limited data set" to be used for other research purposes. If so, the limited data set will only include information that does not directly identify you. For example, the limited data set cannot include your name, address, telephone number, social security number, photographs, or other codes that link you to the information in the limited data set. If limited data sets are created and used, agreements between the parties creating and receiving the limited data set are required in order to protect your identity and confidentiality and privacy.

18. For what study-related purposes will your protected health information be collected, used, and shared with others?

Your PHI may be collected, used, and shared with others to make sure you can participate in the research, through your participation in the research, and to evaluate the results of the research study. More specifically, your PHI may be collected, used, and shared with others for the following study-related purpose(s):

- To learn whether an anti-tumor vaccine can be administered safely and whether the vaccine can stimulate your immune system to fight off the tumor cells in your brain.

Once this information is collected, it becomes part of the research record for this study.

19. Who will be allowed to collect, use, and share your protected health information?

Only certain people have the legal right to collect, use and share your research records, and they will protect the privacy and security of these records to the extent the law allows. These people include:

- The study Principal Investigator (listed in question 3 of this form) and research staff associated with this project.
- Other professionals at the University of Florida or Shands Hospital that provide study-related treatment or procedures.
- The University of Florida Institutional Review Board (IRB; an IRB is a group of people who are responsible for looking after the rights and welfare of people taking part in research).

20. Once collected or used, who may your protected health information be shared with?

Your PHI may be shared with:

- The study sponsor (listed in Question 4 of this form)
- The Moffitt Clinical Research Network, Moffitt Cancer Center, who is coordinating this study
- Members of the Moffitt Cancer Center workforce who provides services in connection with this study.
- The National Cancer Institute (NCI) of National Institutes of Health (NIH), who previously funded this study.
- The person who is responsible for the study nationwide (study chairperson).
- Any laboratories, individuals, and organizations that use your health information in connection with this study.
- The designated Protocol Review and Monitoring Committees, Institutional Review Boards such as Chesapeake IRB, Privacy Boards, Data and Safety Monitoring Board and their related staff that have oversight responsibilities for this study.

- United States agencies who are responsible for overseeing research, such as the Food and Drug Administration, the Department of Health and Human Services, and the Office of Human Research Protections.
- Government agencies who are responsible for overseeing public health concerns such as the Centers for Disease Control and federal, state and local health departments.
- Your insurance company for purposes of obtaining payment

Otherwise, your research records will not be released without your permission unless required by law or a court order. It is possible that once this information is shared with authorized persons, it could be shared by the persons or agencies who receive it and it would no longer be protected by the federal medical privacy law.

21. If you agree to take part in this research study, how long will your protected health information be used and shared with others?

Your PHI will be used and shared with others until the end of the study.

You are not required to sign this consent and authorization or allow researchers to collect, use and share your PHI. Your refusal to sign will not affect your treatment, payment, enrollment, or eligibility for any benefits outside this research study. However, you cannot participate in this research unless you allow the collection, use and sharing of your protected health information by signing this consent and authorization.

You have the right to review and copy your protected health information. However, we can make this available only after the study is finished.

You can revoke your authorization at any time before, during, or after your participation in this study. If you revoke it, no new information will be collected about you. However, information that was already collected may still be used and shared with others if the researchers have relied on it to complete the research. You can revoke your authorization by giving a written request with your signature on it to the Principal Investigator.

SIGNATURES

As an investigator or the investigator's representative, I have explained to the participant the purpose, the procedures, the possible benefits, and the risks of this research study; the alternative to being in the study; and how the participant's protected health information will be collected, used, and shared with others:

_____ _____

Signature of Person Obtaining Consent & Authorization Date

Consenting Adults. You have been informed about this study's purpose, procedures, possible benefits, and risks; the alternatives to being in the study; and how your protected health information will be collected, used and shared with others. You have received a copy of this Form. You have been given the opportunity to ask questions before you sign, and you have been told that you can ask other questions at any time.

Adult Consenting for Self. By signing this form, you voluntarily agree to participate in this study. You hereby authorize the collection, use and sharing of your protected health information as described in sections 17-21 above. By signing this form, you are not waiving any of your legal rights.

_____ _____

Signature of Adult Consenting & Authorizing for Self Date

Parent/Adult Legally Representing the Subject. By signing this form, you voluntarily give your permission for the person named below to participate in this study. You hereby authorize the collection, use and sharing of protected health information for the person named below as described in sections 17-21 above. You are not waiving any legal rights for yourself or the person you are legally representing. After your signature, please print your name and your relationship to the subject.

_____ _____

Consent & Authorization Signature of Parent/Legal Representative Date

_____ _____

Print: Name of Legal Representative Print: Relationship to Participant

_____

Print: Name of Subject

Participants Who Cannot Consent But Can Read and/or Understand about the Study. Although legally you cannot "consent" to be in this study, we need to know if you want to take part. If you decide to take part in this study, and your parent or the person legally responsible for you gives permission, you both need to sign. Your signing below means that you agree to take part (assent). The signature of your parent/legal representative above means he or she gives permission (consent) for you to take part.

_____ _____

Assent Signature of Participant Date